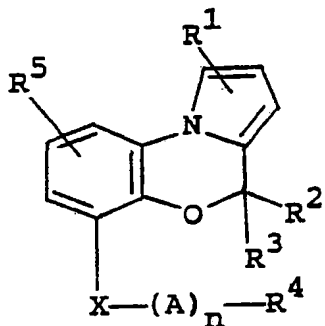




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**(54) Title:** PYRROLOBENZOXAZINE DERIVATIVES AS 5-HT AGONISTS AND ANTAGONISTS**(57) Abstract**

This invention relates to pyrrolobenzoxazine derivatives represented by formula (I), wherein  $R^1$  is hydrogen, etc.,  $R^2$  and  $R^3$  are each lower alkyl, etc.,  $R^4$  is azabicyclo( $C_5-C_{12}$ )alkyl which may be substituted with lower alkyl, etc.,  $R^5$  is halogen, etc., X is  $\alpha$ , etc., A is lower alkylene and n is an integer of 0 or 1. The object compounds and pharmaceutically acceptable salt thereof have pharmacological activities such as 5-HT antagonism and agonism.

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## DESCRIPTION

## PYRROLOBENZOXAZINE DERIVATIVES AS 5-HT AGONISTS AND ANTAGONISTS

5

## Technical Field

The present invention relates to novel pyrrolobenzoxazine derivatives and a pharmaceutically acceptable salt thereof. More particularly, it relates to novel pyrrolobenzoxazine derivatives and a pharmaceutical acceptable salt thereof which have pharmacological activities such as 5-hydroxytryptamine (5-HT) antagonism and agonism and the like, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide novel pyrrolobenzoxazine derivatives and a pharmaceutically acceptable salt thereof, which are useful as a potent and selective antagonist and agonist of 5-HT receptor.

Another object of the present invention is to provide processes for preparation of said pyrrolobenzoxazine derivatives or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said pyrrolobenzoxazine derivatives or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said pyrrolobenzoxazine derivatives or a pharmaceutically acceptable salt thereof as a 5-HT antagonist useful for treating or preventing central nervous system (CNS) disorders such as psychosis (e.g. schizophrenia, mania, etc.), anxiety, and depression;

pains or aches such as headaches (e.g. migraine, cluster headaches, vascular headaches, etc.) and neuralgia (e.g. trigeminal neuralgia, etc.); gastrointestinal disorders such as symptoms of gastrointestinal dysfunction such as occur with, for example, dyspepsia, peptic ulcer, reflux oesophagitis and flatulence, and irritable bowel syndrome (IBS); nausea or vomiting, each of which may be associated with cancer therapy; motion sickness; and the like in human being or animals, particularly nausea and vomiting, and as a 5-HT agonist useful for treating or preventing gastrointestinal disorders such as constipation (irritable bowel syndrome, etc.), dyspepsia, reflux oesophagitis, nausea or vomiting and the like in human being or animals.

15

## Background Art

20

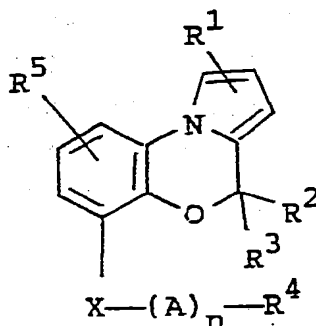
4H-Pyrrolo[2,1-c][1,4]benzoxazines characterized by having an alkylamine substituent at 4th position are disclosed in the United States Patent No. 4035495 and the US Patent also disclosed that said compounds possess antihypertensive and central nervous system depressant activity.

25

## Disclosure of the invention

The pyrrolobenzoxazine derivatives of the present invention are novel and can be represented by the formula [I] :

30



35

[I]

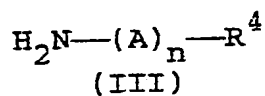
wherein R<sup>1</sup> is hydrogen or halogen,  
R<sup>2</sup> and R<sup>3</sup> are each hydrogen or lower alkyl,  
R<sup>4</sup> is lower alkylamino;  
azabicyclo(C<sub>5</sub>-C<sub>12</sub>)alkyl which may be  
substituted with lower alkyl; or  
N-containing heterocyclic group  
which may be substituted with ar(lower)-  
alkyl optionally substituted with halogen,  
R<sup>5</sup> is hydrogen, halogen, lower alkyl, acyl or  
acylamino,  
X is  $\begin{array}{c} | \\ \text{CONH-} \end{array}$  or  $\begin{array}{c} | \\ \text{NHCONH-} \end{array}$ ,  
A is lower alkylene and  
n is an integer of 0 or 1.

With regard to the compound [I] of the present invention, it is to be noted that there may be one or more optically or geometrically isomeric pairs due to the presence of one or more asymmetric carbon atom(s) and these isomers or a mixture thereof are included within a scope of the compound [I] of the present invention.

Particularly, the compound [I] of the present invention may adopt an endo or exo configuration, and in such a case, the endo configuration is preferred.

The optical and geometrical isomers may be separated one from the other by the usual manners.

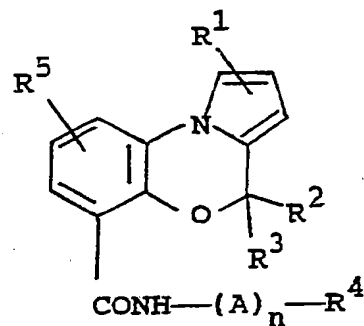
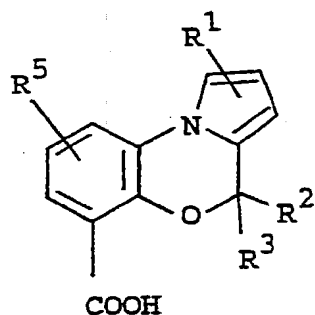
According to the present invention, the object compound [I] can be prepared by the following processes.

Process 1 :

or its reactive  
derivative  
at the amino  
group  
or its salt

5

10



15

[II]

or its reactive derivative  
at the carboxy group  
or its salt

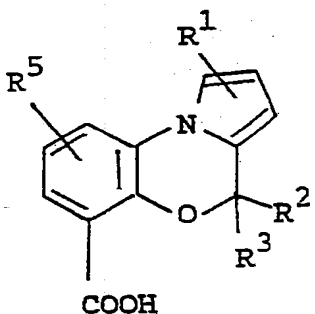
[Ia]

or its salt

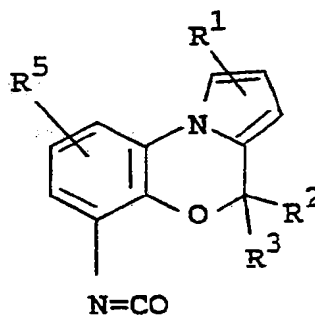
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Process 2

25



rearrangement



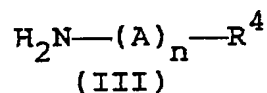
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[II]

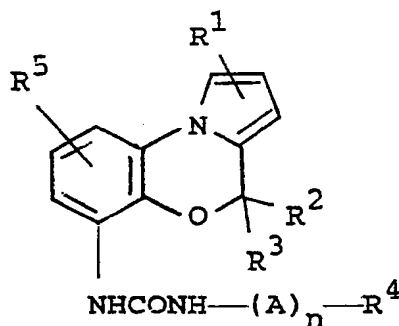
or its reactive derivative  
at the carboxy group  
or its salt

[XII]

35



or its reactive  
derivative  
at the amino  
group  
or its salt



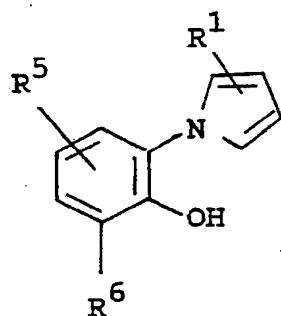
[Ib]

or its salt

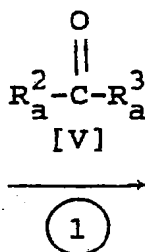
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are each as defined  
above.

The starting compound [II] in the above process is  
novel and can be prepared by the following processes.

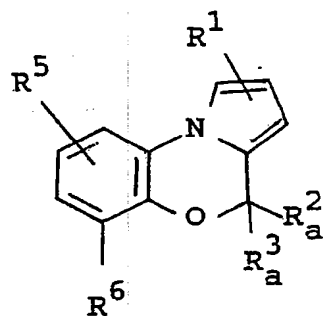
#### Process A



[IV]



(1)

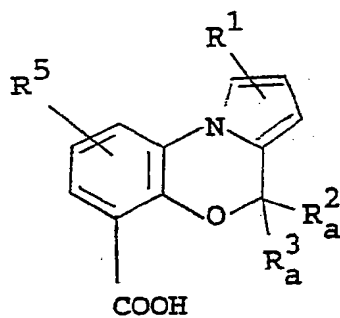


[VI]

elimination of  
carboxy protective  
group

5

(2)



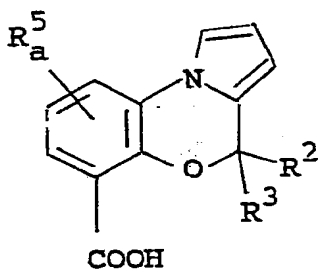
[IIa]

or its salt

10

Process B

15

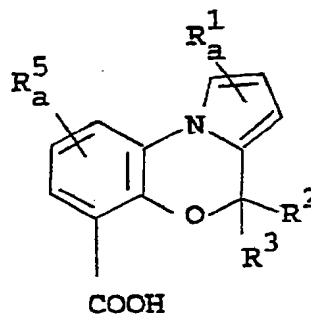


20

[IIb]

or its salt

halogenation



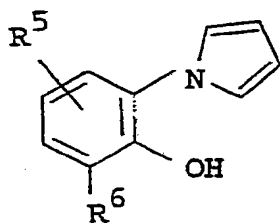
[IIc]

or its salt

25

Process C

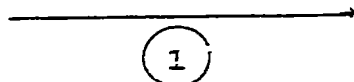
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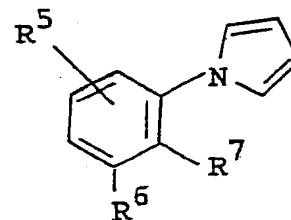
[IVa]

35

introduction of  
hydroxy protective  
group

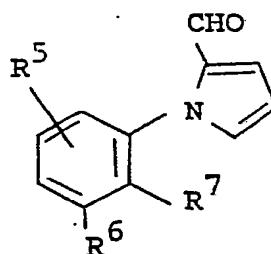
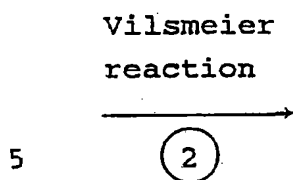


(1)

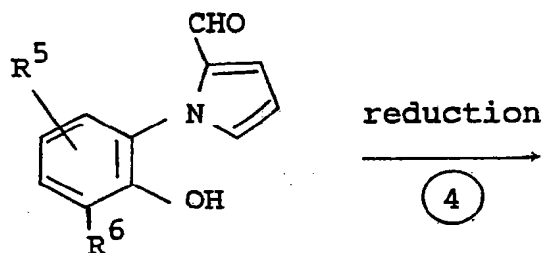
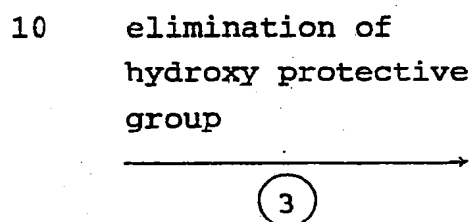


[VII]

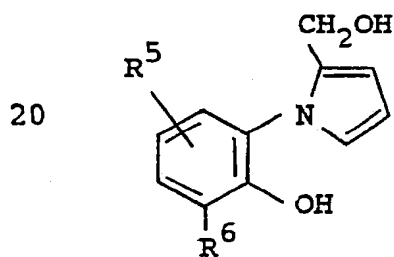




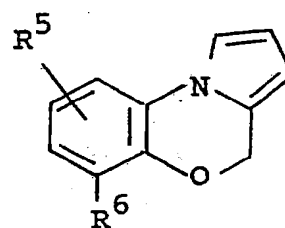
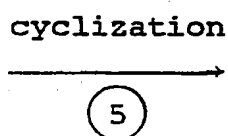
[VIII]



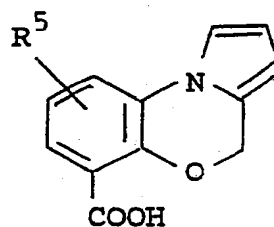
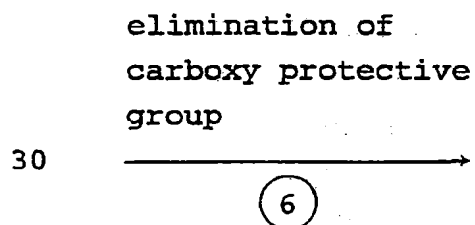
[IX]



[X]



[XI]



[IId]

or its salt

35

wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^5$  are each as defined above,  
     $R_a^1$  is halogen,  
     $R_a^2$  and  $R_a^3$  are lower alkyl,  
     $R_a^5$  is halogen,  
5      $R_a^6$  is protected carboxy and  
     $R^7$  is protected hydroxy.

10     In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

    The term "lower" is intended to mean 1 to 6 carbon atoms unless otherwise indicated.

15     Suitable "lower alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like.

20     Suitable "lower alkyl" moiety in the term "(lower)alkylamino" can be referred to the ones as exemplified above.

    Suitable "lower alkylamino" may include "mono(lower)alkylamino" [e.g. methylamino, ethylamino, isopropylamino, hexylamino, etc.] and  
25     "di(lower)alkylamino" [e.g. dimethylamino, diethylamino, dipropylamino, methylethylamino, etc.] and the like.

30     Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, dimethylethylene, hexamethylene, and the like.

    Suitable "halogen" may include chlorine, bromine, iodine and fluorine.

    Suitable "ar(lower)alkyl" may include benzyl, phenethyl, benzhydryl, trityl and the like.

35     Suitable "azabicyclo( $C_5-C_{12}$ )alkyl may include

azabicyclo[3,2,1]octyl, azabicyclo[2,2,2]octyl, azabicyclo[3,3,1]nonyl, and the like, which may be substituted by lower alkyl as stated above (e.g. methyl, ethyl, etc.) preferably azabicyclo(C<sub>7</sub>-C<sub>10</sub>)alkyl which may be substituted with lower alkyl, more preferably azabicyclooctyl which may be substituted with lower alkyl.

Suitable "protected carboxy" may include carbamoyl; acylcarbamoyl such as lower alkylsulfonylcarbamoyl (e.g., methylsulfonylcarbamoyl, ethylsulfonylcarbamoyl, propylsulfonylcarbamoyl, isopropylsulfonylcarbamoyl, butylsulfonylcarbamoyl, t-butylsulfonylcarbamoyl, pentylsulfonylcarbamoyl, t-pentylsulfonylcarbamoyl, hexylsulfonylcarbamoyl, etc.), arylsulfonylcarbamoyl (e.g., phenylsulfonylcarbamoyl, naphthylsulfonylcarbamoyl, etc.) and the like; esterified carboxy in which said ester may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.), lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g., 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, 1-acetoxypropyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-acetoxyethyl ester, 2-propionyloxyethyl ester, 1-isobutyryloxyethyl ester, etc.), lower alkanesulfonyl(lower)alkyl ester (e.g., mesylmethyl ester, 2-mesyloethyl ester, etc.), ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester which may be substituted with one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester,

diphenylmethyl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-ditertiarybutylbenzyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, 5 ethoxycarbonyloxymethyl ester, ethoxycarbonyloxyethyl ester, etc.), aroyloxy(lower)alkyl ester (e.g., benzoyloxymethyl ester, benzoyloxyethyl ester, toluoyloxyethyl ester, etc.), aryl ester which may have one or more suitable substituent(s) (e.g., phenyl ester, 10 tolyl ester, tertiarybutylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); and the like.

Suitable "protected hydroxy" may include acyloxy such as lower alkanoyloxy having 1 to 6 carbon atoms (e.g. 15 formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isobavoryloxy, pivaloyloxy, hexanoyloxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.) or the like, and the like.

Suitable "N-containing heterocyclic group" may include unsaturated 5- or 6-membered heteromonocyclic 20 group containing 1 or 2 nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, 1,2,3,6-tetrahydropyridyl, etc.;

saturated 5- or 6-membered heteromonocyclic group containing 1 or 2 nitrogen atom(s) and/or 1 or 2 oxygen 25 atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, morpholinyl, etc.;

saturated 5- or 6-membered heteromonocyclic group containing 1 or 2 nitrogen atom(s) and 1 or 2 sulfur 30 atom(s), for example, thiazolidinyl, thiomorpholinyl, etc., and the like.

Suitable acyl may include an aliphatic acyl, an aromatic acyl and an aliphatic acyl substituted with aromatic group(s).

The aliphatic acyl may include saturated or 35 unsaturated, acyclic or cyclic ones, such as lower

alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), lower alkanesulfonyl [e.g. methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, pentanesulfonyl, hexanesulfonyl, etc.], lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), carbamoyl and the like.

The aromatic acyl may include aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.) and the like.

The aliphatic acyl substituted with aromatic group(s) may include ar(lower)alkanoyl such as phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), ar(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethylloxycarbonyl, etc.), phenoxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.), and the like.

Suitable example of "acyl" moiety in the term of "acylamino" can be referred to the ones as exemplified above. Suitable "acylamino" may include lower alkanoylamino (e.g. formylamino, acetylamino, etc.) and the like.

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate etc.], a salt with an amino acid [e.g. arginine salt, ornithine salt, etc.], or the like, and the like.

Suitable pharmaceutically acceptable salts of the starting compound [II] are conventional non-toxic salts and include a salt with base such as alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline

earth metal salt [e.g. calcium salt, magnesium salt, etc.] or the like, and the like.

The processes for preparing the object compounds [I] of the present invention are explained in detail in the following.

#### Process 1

The object compound [Ia] or its salt can be prepared by reacting the compound [II] or its reactive derivative at the carboxy group or its salt with the compound [III] or its reactive derivative at the amino group or its salt.

Suitable reactive derivative at the carboxy group of the compound [II] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl  $[(CH_3)_2N^+=CH-]$  ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester,

carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.] or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound [II] to be used.

Suitable salt of the reactive derivative of the compound [II] can be referred to the salt as exemplified for the compound [I].

Suitable reactive derivative at the amino group of the compound [III] may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound [III] with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound [III] with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound [III] with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound [III] and its reactive derivative can be referred to the salt as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene dichloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [II] is used in a free acid form or its salt form, the reaction is

preferably carried out in the presence of a conventional  
condensing agent such as N,N'-dicyclohexylcarbodiimide;  
N-cyclohexyl-N'-morpholinoethylcarbodiimide;  
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;  
5 N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide;  
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;  
N,N'-carbonylbis-(2-methylimidazole);  
pentamethyleneketene-N-cyclohexylimine;  
diphenylketene-N-cyclohexylimine; ethoxyacetylene;  
10 1-alkoxy-1-chloroethylene; trialkyl phosphite, ethyl  
polyphosphate; isopropyl polyphosphate; phosphorus  
oxychloride (phosphoryl chloride); phosphorus trichloride;  
diphenyl phosphorylazide; diphenylphosphoinic chloride;  
thionyl chloride; oxalyl chloride; lower alkyl haloformate  
15 [e.g. ethyl chloroformate, isopropyl chloroformate, etc.];  
triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt;  
2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide  
intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-  
chloro-1H-benzotriazole; so-called Vilsmeier reagent  
20 prepared by the reaction of N,N-dimethylformamide with  
thionyl chloride, phosgene, trichloromethyl chloroformate,  
phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence  
of an inorganic or organic base such as an alkali metal  
25 bicarbonate, tri(lower)alkylamine, pyridine,  
N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine,  
or the like.

The reaction temperature is not critical, and the  
reaction is usually carried out under cooling, at ambient  
30 temperature or under warming.

## Process 2

### (1) Preparation of an intermediate compound [XII]

The intermediate compound [XII] can be prepared by  
35 subjecting a compound [II] or its reactive derivative at



the carboxy group or its salt to rearrangement reaction.

Suitable reactive derivative at the carboxy group of the compound [II] can be referred to those as exemplified in Process 1.

5        Suitable rearrangement reaction can include Curtius rearrangement, Lossen rearrangement, Hofmann rearrangement, etc..

10        In the Curtius rearrangement, the intermediate compound [XII] can be prepared by reacting a compound [II] or its reactive derivative at the carboxy group or its salt with an azide derivative.

Suitable azide derivative may include diphenyl phosphoroazidate, sodium azide, etc..

15        This reaction is usually carried out in a conventional solvent such as chloroform, methylene chloride, carbon tetrachloride, toluene, water, methanol, ethanol, N,N-dimethylformamide or the like.

The reaction temperature is not critical, and the reaction is usually carried out under warming or heating.

20        The intermediate compound [XII] may be used without isolation for the next reaction.

## (2) Preparation of the object compound [Ib]

25        The object compound [Ib] or its salt can be prepared by reacting the compound [XII] with the compound [III] or its reactive derivative at the amino group or its salt.

Suitable reactive derivative at the amino group of the compound [III] can be referred to those as exemplified in Process 1.

30        The reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. base, condensing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

35        It is to be noted that the compounds [Ia] and [Ib] are

included within the scope of the compound [I], and accordingly the suitable salts of these compounds [Ia] and [Ib] are to be referred to those as exemplified for the compound [I] in the above.

5

Process A - (1)

The compound [VI] can be prepared by reacting the compound [IV] with the compound [V].

10 The reaction is usually carried out in a conventional solvent such as dichloromethane, benzene or any other solvent which does not adversely influence the reaction.

The reaction is preferably carried out in the presence of inorganic or organic acid.

15 Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

20 The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process A - (2)

25 The compound [IIa] or its salt can be prepared by subjecting the compound [VI] to elimination reaction of the carboxy protective group.

The present reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

30 In case that the protective group is an ester, the protective group can be eliminated by hydrolysis. Hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline  
35 earth metal (e.g. magnesium, calcium, etc.), the hydroxide

or carbonate or bicarbonate thereof, trialkylamine (e.g. trimethylamine, triethylamine, etc.), or the like.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

Reduction can be applied preferably for elimination of the protective group such as 4-nitrobenzyl, 2-iodoethyl, 2,2,2-trichloroethyl, or the like. The reduction method applicable for the elimination reaction may include, for example reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chrome compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium-carbon, etc.).

The reaction is usually carried out in a solvent such as water, an alcohol (e.g. methanol, ethanol, etc.), methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

#### Process B

The compound [IIc] or its salt can be prepared by halogenating the compound [IIb] or its salt.

Suitable halogenating agent of this reaction may include conventional ones for example, halogen [e.g. chlorine, bromine iodine, etc.], sulfuryl halide [e.g. sulfuryl chloride, sulfuryl bromide, etc.], N-halosuccinimide [e.g. N-chlorosuccinimide, N-bromosuccinimide, etc.], pyridinium hydrohalide

perhalide [e.g. pyridinium hydrobromide perbromide, pyridinium hydrochloride perchloride, etc.] quaternary ammonium perhalide [e.g. phenyltrimethylammonium perbromide, etc.],  $\omega$ -trihaloacetophenone [e.g.  $\omega$ -tribromoacetophenone, etc.], cupric or potassium bromide, selenium oxychloride, or the like. These halogenating agents may be selected according to the kind of the starting compound [IIb] to be used.

This reaction is usually carried out in a conventional solvent such as chloroform, methylene chloride, carbon tetrachloride, acetic acid, a mixture of hydrogen halide [e.g. hydrogen bromide, hydrogen chloride, etc.] and acetic acid, water, N,N-dimethylformamide or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming or heating.

#### Process C - (1)

The compound [VII] can be prepared by subjecting the compound [IVa] to introduction reaction of the hydroxy protective group.

The agents used in this reaction may be one which is capable of introducing the hydroxy protective group as exemplified before such as a conventional acylating agent, or the like.

Suitable acylating agent may include an organic acid as exemplified in the explanation of the above Process A - (2) or its reactive derivative.

The suitable reactive derivative of the organic acid may be a conventional one such as an acid halide (e.g. acid chloride, acid bromide, etc.), an acid azide, an acid anhydride, an activated amide, an activated ester, an isocyanate [e.g. aryl isocyanate (e.g. phenyl isocyanate, etc.), etc.].

When free acid is used as an acylating agent, the acylation reaction may preferably be conducted in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide or the like.

5 This reaction is usually carried out in a solvent which does not adversely influence the reaction such as methanol, ethanol, propanol, dichloromethane, pyridine, tetrahydrofuran, chloroform and the like.

10 The reaction temperature is not critical and the reaction can be carried out under cooling to under heating.

#### Process C - (2)

15 The compound [VIII] can be prepared by subjecting the compound [VII] to Vilsmeier reaction.

Vilsmeier reaction is carried out in the presence of N,N-dimethylformamide and phosphorus oxyhalide [e.g. phosphorus oxychloride, etc.] or phosgene, etc.

20 The reaction is usually carried out in a conventional solvent such as, water, acetone, dioxane, acetonitrile, ethylene chloride, tetrahydrofuran, diethyl ether or any other organic solvent which does not adversely influence the reaction. The N,N-dimethylformamide can also be used as the solvent.

25 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

#### Process C - (3)

30 The compound [IX] can be prepared by subjecting the compound [VIII] to elimination reaction of the hydroxy protective group.

The present elimination reaction is carried out in accordance with a conventional method such as hydrolysis; reduction; or the like as explained in Process A - (2).

35 Therefore, the reaction mode and reaction conditions

[e.g. acid, base, reducing agent, solvent, reaction temperature, etc.] or this reaction are to be referred to those as explained in Process A - (2).

5 Process C - (4)

The compound [X] can be prepared by reducing the compound [IX].

10 The reaction including chemical reduction and catalytic reduction, may be carried out in a conventional manner.

Suitable reducing agents to be used in chemical reduction are a metal [e.g. tin, zinc, iron, etc.], a combination of such metal and/or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic  
15 or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.],  
a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride,  
20 aluminum hydride, lithium trimethoxyaluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, borane, diborane, etc.], a phosphorus compound [e.g.  
25 phosphorus trichloride, phosphorus tribromide, triphenylphosphine, triethylphosphine, etc.] and the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal  
30 platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel,  
35 nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g.

reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.], or the like.

- 5       The reduction is usually carried out in a solvent. A suitable solvent to be used may be water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetonitrile or any other conventional organic solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.
- 10       Additionally, the aforementioned liquid acids to be used in chemical reduction can also be used as a solvent.

The reaction is preferably carried out under cooling to warming.

15       Process C - (5)

The compound [XI] can be prepared by subjecting the compound [X] to cyclization reaction.

This cyclization reaction is carried out in the presence of a dehydrating agent.

- 20       Suitable dehydrating agents used of this reaction may include conventional organic or inorganic ones such as an inorganic halogen compound [e.g. thionyl chloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, stannic chloride, titanium
- 25       tetrachloride, etc.]; sulfonyl halide [e.g. mesyl chloride, tosyl chloride, benzenesulfonyl chloride, etc.]; carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.];
- 30       other phosphorus compound [e.g. phosphorus pentoxide, polyphosphate ester, etc.]; a combination of phosphine compound [e.g. triethylphosphine, triphenylphosphine, etc.] and azodicarboxylate ester compound [e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.]; and
- 35       the like or an optional mixture thereof.

This reaction is usually carried out in a conventional solvent such as diethyl ether, N,N-dimethylformamide, pyridine, acetic acid, formic acid, benzene, carbon tetrachloride, chloroform, methylene chloride, tetrahydrofuran, dioxane, sulfolane, and the like. Additionally in case that the above-mentioned dehydrating agents are in liquid, they can also be used as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under cooling to under heating.

#### Process C - (6)

The compound [IIId] or its salt can be prepared by subjecting the compound [XI] to elimination reaction of the carboxy protective group. The reaction can be carried out in substantially the same manner as Process A - (2), and therefore the reaction mode and reaction conditions [e.g. acid, base reducing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process A - (2).

In this respect, it is to be noted that the compounds [IIa] to [IIId] are included within the scope of the compound [II], and accordingly the suitable salts of these compounds [IIa] to [IIId] are to be referred to those as exemplified for the compound [II] in the above.

The compounds thus obtained by Processes 1 and 2 and Processes A - (2), B and C - (6) may be converted into aforesaid pharmaceutically acceptable salts thereof according to a conventional manner.

The object compound [I] of the present invention can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.



The object compound [I] of the present invention are novel and exhibit pharmacological activities such as 5-HT antagonism, especially, 5-HT<sub>3</sub> antagonism, and 5-HT agonism, especially, 5-HT<sub>4</sub> agonism and the like and therefore are useful as 5-HT antagonist and agonist for treating or preventing central nervous system (CNS) disorders such as psychosis (e.g. schizophrenia, mania, etc.), anxiety, and depression; pains or aches such as headaches (e.g. migraine, cluster headaches, vascular headaches, etc.), and neuralgia (e.g. trigeminal neuralgia, etc.); gastrointestinal disorders such as symptoms of gastrointestinal dysfunction such as occur with, for example, dyspepsia, peptic ulcer, reflux oesophagitis and flatulence, and irritable bowel syndrome (IBS); nausea or vomiting, each of which may be associated with cancer therapy; motion sickness; constipation and the like.

Further, it is expected that the object compound [I] of the present invention are useful as therapeutical and/or preventive agents for obesity; lung embolism; arrhythmia; withdrawal syndrome resulting from addition to a drug or substance of abuse; stress-related psychiatric disorders; rhinitis; and serotonin-induced nasal disorders, and the like.

In order to illustrate the usefulness of the object compound [I], pharmacological activities of representative compound of the present invention are shown below.

(1) Inhibition of Benzold-Jarisch reflex

Test Method :

Male Sprague-Dawley rats weighing 260-350 g were anesthetized intraperitoneally with 1.25 g/kg urethane.

Blood pressure and heart rate were monitored continuously from the left common carotid artery with a pressure transducer. A right femoral vein was cannulated

for the intravenous injection (iv) of drugs. The trachea was also cannulated to ease the respiration.

Rats were given a rapid bolus injection of 2-methyl-5-hydroxytryptamine (32 µg/kg, iv) to establish the control bradycardic response. Once the heart rate returned to base line, the rats were given the test compound (iv), followed by 5-minutes interval and another bolus injection of 2-methyl-5-hydroxytryptamine (32 µg/kg, iv).

Test Result :

Test Compound	Dose (µg/kg)	Inhibition (%)
Example 1	3.2	68.1
Example 2(1)	3.2	76.3
Example 3(1)	3.2	81.8
Example 3(2)	3.2	70.8

(2) Inhibition of Cisplatin-induced vomiting

Test Method :

Nonfasted female beagles weighing about 10 kg were administered test compound or saline intravenously twice 10 minutes prior to and 90 minutes after Cisplatin dosing (3.2 mg/kg, iv).

Cisplatin was dissolved in 0.9% warm saline with a final concentration of 3 mg/ml and used immediately. The beagles were observed for vomiting for up to 5 hours following Cisplatin administration.

Test Result :

Test compound	Dose ( $\mu\text{g/kg}$ )	Inhibition (%)
Example 1	100	96.3
Example 2(1)	100	81.5

10 (3) Contractile response on isolated ileum of guinea pigTest Method :

Isolated strips of guinea pig ileum were set up in chambers containing Tyrode solution (37°C) with a resting tension of 0.3~0.6 g.

15 After the contractile activities were observed with 5-hydroxytryptamine (5-HT)( $10^{-5}\text{M}$ ), the response to the respective compounds ( $10^{-5}\text{M}$ ) was examined.

Test Result :

20

Test compound	Contractile response (%)
Example 1	57.1
Example 2(1)	72.4
5-HT	100

25

For therapeutic administration, the object compound  
30 [I] of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for  
35 oral, parenteral and external administration. The

pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

5           If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid  
10           magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

          While the dosage of the compound [I] may vary from and also depend upon the age, conditions of the patient, a kind of diseases or conditions, a kind of the compound [I]  
15           to be applied, etc. In general amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 10 mg, 20 mg, 50 mg, 100 mg  
20           of the object compound [I] or the present invention may be used in treating diseases.

          The following Preparations and Examples are given for the purpose of illustrating the present invention.

25           Preparation 1

          A mixture of ethyl 3-amino-5-chloro-2-hydroxybenzoate (7.02 g), 2,5-dimethoxytetrahydrofuran (6.45 g), dioxane (40 ml), and acetic acid (25 ml) was heated at 100°C for 3.5 hours. The reaction mixture was evaporated in vacuo,  
30           and the residue was diluted with methylene chloride. The methylene chloride solution was washed successively with aqueous sodium bicarbonate solution, water, and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel,  
35           using chloroform-hexane (1:1) mixture as eluent to give

ethyl 5-chloro-2-hydroxy-3-(pyrrol-1-yl)benzoate (8.50 g).

mp : 106-107°C

IR (Nujol) : 1675, 1585  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.44 (3H, t,  $J=7.2\text{Hz}$ ), 4.45 (2H, q,  $J=7.2\text{Hz}$ ), 6.34 (2H, m), 7.05 (2H, m), 7.46 (1H, d,  $J=2.6\text{Hz}$ ), 7.77 (1H, d,  $J=2.6\text{Hz}$ ), 11.40 (1H, s)

### Preparation 2

10 A mixture of ethyl 5-chloro-2-hydroxy-3-(pyrrol-1-yl)benzoate (18 g), p-toluenesulfonic acid monohydrate (1.7 g), acetone (150 ml), and benzene (950 ml) was heated at 70°C for 72 hours. After cooling, the reaction mixture was washed with water and brine, dried over anhydrous  
15 magnesium sulfate, and evaporated in vacuo. The residual oil was chromatographed on silica gel, using dichloromethane-hexane (1:1) mixture as eluent to give ethyl 8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxylate (14.6 g) as an oil.

20 IR (Neat) : 1725, 1710, 1675, 1590, 1555, 1490  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.40 (3H, t,  $J=7\text{Hz}$ ), 1.64 (6H, s), 4.37 (2H, q,  $J=7\text{Hz}$ ), 6.02 (1H, m), 6.33 (1H, t,  $J=3\text{Hz}$ ), 7.05 (1H, m), 7.42 (1H, d,  $J=2\text{Hz}$ ), 7.52 (1H, d,  $J=2\text{Hz}$ )

25

### Preparation 3

A mixture of ethyl 8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylate (640 mg), aqueous 3N sodium hydroxide (4 ml), and ethanol (5 ml) was  
30 stirred at room temperature for 3 hours. After evaporation of the solvent, the residue was diluted with water and washed with dichloromethane. The aqueous layer was made acidic with 3N hydrochloric acid and extracted three times with dichloromethane. The organic layer was  
35 washed with water and brine, dried over anhydrous

magnesium sulfate, and evaporated in vacuo. The residue obtained was recrystallized from ethyl acetate-hexane to give 8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxylic acid (413 mg).

5 mp : 184-187°C  
IR (Nujol) : 3230, 1742, 1595, 1490 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ) : 1.57 (6H, s), 6.12 (1H, m), 6.30 (1H, m), 7.43 (1H, m), 7.58 (1H, m), 8.01 (1H, m), 13.16 (1H, br s)

10

#### Preparation 4

A mixture of ethyl 5-chloro-2-hydroxy-3-(pyrrol-1-yl)benzoate (1.0 g), acetic anhydride (1 ml), pyridine (1 ml), and dichloromethane (5 ml) was stirred at room temperature for 40 hours. After evaporation of the solvent, the oily residue was diluted with toluene and evaporated in vacuo. This operation was repeated three times in order to remove pyridine and acetic anhydride. There was obtained 1.16 g of ethyl 2-acetoxy-5-chloro-3-(pyrrol-1-yl)benzoate as an oil, which was used in the next reaction without further purification.

20 IR (Film) : 1775, 1725, 1585, 1490 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 1.38 (3H, t, J=7Hz), 2.21 (3H, s), 4.35 (2H, q, J=7Hz), 6.32 (2H, m), 6.85 (2H, m), 7.54 (1H, d, J=2Hz), 7.94 (1H, d, J=2Hz)

25

#### Preparation 5

Phosphorus oxychloride (0.42 ml) was added dropwise to N,N-dimethylformamide (0.357 g) cooled to 0°C. The mixture was stirred at 0°C for 10 minutes and then at room temperature for 15 minutes. To this mixture cooled to 0°C, were added 1,2-dichloroethane (5 ml) and a solution of ethyl 2-acetoxy-5-chloro-3-(pyrrol-1-yl)benzoate (1.1 g) in 1,2-dichloroethane (9 ml). The mixture was stirred at room temperature for 20 minutes and at 70°C for 1 hour.

35

The reaction mixture was treated with a solution of sodium acetate trihydrate (4.3 g) in water (20 ml) and stirred at 60°C for 20 minutes. After cooling, the reaction mixture was extracted twice with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Column chromatography on silica gel (1% methanol-dichloromethane) gave ethyl 2-acetoxy-5-chloro-3-(2-formylpyrrol-1-yl)benzoate (0.82 g) as crystals.

10 mp : 125-128°C  
IR (Nujol) : 1765, 1725, 1660, 1585, 1525 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 1.37 (3H, t, J=7Hz), 2.06 (3H, s),  
4.34 (2H, q, J=7Hz), 6.41 (1H, m), 6.92 (1H, m),  
7.10 (1H, m), 7.55 (1H, d, J=2Hz), 8.09 (1H, d,  
15 J=2Hz), 9.52 (1H, s)

#### Preparation 6

To a mixture of ethyl 2-acetoxy-5-chloro-3-(2-formylpyrrol-1-yl)benzoate (0.791 g), ethanol (10 ml), and tetrahydrofuran (8 ml) at room temperature was added 28% sodium methoxide in methanol (0.6 ml). After being stirred for 30 minutes, the reaction mixture was treated with a mixture of acetic acid and water (1:1, 6 ml) and evaporated in vacuo. The residue was diluted with water and extracted twice with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated. Column chromatography on silica gel (dichloromethane-hexane, 1:1) of the residue gave ethyl 5-chloro-2-hydroxy-3-(2-formylpyrrol-1-yl)benzoate (230 mg).

30 mp : 105-110°C  
IR (Nujol) : 3100, 2720, 1675, 1610, 1590, 1530 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 1.44 (3H, t, J=7Hz), 4.43 (2H, q, J=7Hz), 6.45 (1H, m), 6.99 (1H, s), 7.14 (1H, m),  
35 m), 7.46 (1H, m), 7.46 (1H, d, J=2Hz), 7.91 (1H,

d, J=2Hz), 9.54 (1H, s), 11.20 (1H, s)

#### Preparation 7

To a mixture of ethyl 5-chloro-2-hydroxy-3-(2-formylpyrrol-1-yl)benzoate (2.75 g), tetrahydrofuran (15 ml), and ethanol (15 ml) at 0°C was added in small portions sodium borohydride (0.70 g) over a period of 1 hour. After being stirred for 30 minutes, the reaction mixture was evaporated in vacuo. The residue was diluted with water, made acidic with aqueous oxalic acid, and extracted with chloroform. The organic layer was washed successively with aqueous sodium hydrogen carbonate, water, and brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The oily residue obtained (ethyl 5-chloro-2-hydroxy-3-(2-hydroxymethylpyrrol-1-yl)benzoate) was used in the next reaction without further purification.

IR (Film) : 3350, 1680, 1610, 1590  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.45 (3H, t, J=7Hz), 1.87 (1H, t, J=6Hz), 4.44 (2H, d, J=6Hz), 4.46 (2H, q, J=7Hz), 6.30 (1H, m), 6.36 (1H, m), 6.73 (1H, m), 7.55 (1H, d, J=2Hz), 7.91 (1H, d, J=3Hz), 11.39 (1H, s)

#### Preparation 8

To a mixture of crude ethyl 5-chloro-2-hydroxy-3-(2-hydroxymethylpyrrol-1-yl)benzoate, triphenylphosphine (3.68 g), and tetrahydrofuran (30 ml) at 0°C was added a solution of diethyl azodicarboxylate (2.45 g) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 14 hours under a nitrogen atmosphere. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by silica



gel column chromatography (dichloromethane-hexane, 2:1) to give ethyl 8-chloro-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylate (1.16 g).

mp : 90-95°C

5 IR (Nujol) : 1725, 1600, 1565, 1495 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 1.39 (3H, t, J=7Hz), 4.35 (2H, q, J=7Hz), 5.22 (2H, s), 6.10 (1H, m), 6.35 (1H, m), 7.08 (1H, m), 7.44 (1H, d, J=2Hz), 7.52 (1H, d, J=2Hz)

10

#### Preparation 9

The following compound was obtained according to a similar manner to that of Preparation 3.

15 8-Chloro-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylic acid

mp : 200-210°C (CH<sub>2</sub>Cl<sub>2</sub>-toluene)

IR (Nujol) : 2700-2300 1665, 1600, 1560 cm<sup>-1</sup>

20 NMR (DMSO-d<sub>6</sub>, δ) : 5.24 (2H, s), 6.11 (1H, m), 6.33 (1H, m), 7.42 (1H, d, J=2Hz), 7.61 (1H, m), 8.02 (1H, d, J=2Hz), 13.25 (1H, s)

#### Preparation 10

25 A mixture of 8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c]-[1,4]benzoxazine-6-carboxylic acid (3.0 g), N-chlorosuccinimide (1.44 g) in N,N-dimethylformamide (30 ml) was stirred at 0°C for 4 hours and then at room temperature for 14 hours. The reaction mixture was diluted with water and extracted with dichloromethane.

30 The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Recrystallization of the residue from toluene-hexane gave 1,8-dichloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxylic acid (2.28 g).

35 mp : 130-135°C

IR (Nujol) : 2800-2400, 1700, 1675, 1595, 1570  $\text{cm}^{-1}$   
NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.55 (6H, s), 6.22 (1H, d,  $J=4\text{Hz}$ ), 6.41 (1H, d,  $J=4\text{Hz}$ ), 7.54 (1H, d,  $J=2\text{Hz}$ ), 8.22 (1H, d,  $J=2\text{Hz}$ ), 13.23 (1H, s)

5

### Preparation 11

A mixture of ethyl 5-chloro-2-hydroxy-3-(pyrrol-1-yl)benzoate (7.0 g), triethylamine (13.3 g), water (5 ml), and ethanol (80 ml) was hydrogenated over a 10% palladium carbon catalyst (0.7 g) at one atmospheric pressure at room temperature. After 5 hours, the mixture was filtered and then evaporated in vacuo. The residue obtained was crystallized from methanol to give ethyl 2-hydroxy-3-(pyrrol-1-yl)benzoate (2.86 g). The filtrate was concentrated and chromatographed on silica gel (hexane-dichloromethane, 3:2) to give another crop of ethyl 2-hydroxy-3-(pyrrol-1-yl)benzoate (1.29 g) after recrystallization from methanol.

10

15

mp : 56-58°C

20

IR (Nujol) : 1670, 1605, 1585, 1495  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.37 (3H, t,  $J=7.1\text{Hz}$ ), 4.42 (2H, q,  $J=7.1\text{Hz}$ ), 6.23 (2H, t,  $J=2.2\text{Hz}$ ), 7.04 (1H, t,  $J=7.9\text{Hz}$ ), 7.13 (2H, t,  $J=2.2\text{Hz}$ ), 7.64 (1H, dd,  $J=1.6, 7.8\text{Hz}$ ), 7.80 (1H, dd,  $J=1.6, 8.0\text{Hz}$ )

25

### Preparation 12

The following compounds were obtained according to a similar manner to that of Preparation 1.

30

(1) Ethyl 5-methanesulfonyl-2-hydroxy-3-(pyrrol-1-yl)benzoate

mp : 185-188°C (from iPE-n-hexane)

IR (Nujol) : 1695, 1590  $\text{cm}^{-1}$

35

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.40 (3H, t,  $J=7\text{Hz}$ ), 3.31 (3H, s), 4.48 (2H, q,  $J=7\text{Hz}$ ), 6.29 (2H, m), 7.24 (2H,

m), 8.07 (1H, d, J=2.3Hz), 8.22 (1H, d, J=2.3Hz), 11.80 (1H, s)

Elemental Analysis Calcd. for  $C_{14}H_{15}NO_5S$  :

C 54.36%, H 4.89%, N 4.53%

5

Found : C 54.99%, H 4.87%, N 4.33%

(2) Ethyl 5-acetylamino-2-hydroxy-3-(pyrrol-1-yl)benzoate  
mp : 154-155°C (from AcOEt-iPE)

IR (Nujol) : 3350, 1660, 1610, 1565  $cm^{-1}$

10

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.38 (3H, t, J=7Hz), 2.04 (3H, s), 4.41 (2H, q, J=7Hz), 6.24 (2H, m), 7.08 (2H, m), 8.00 (1H, d, J=2.6Hz), 8.12 (1H, d, J=2.6Hz), 10.08 (1H, s), 10.96 (1H, s)

Elemental Analysis Calcd. for  $C_{15}H_{16}N_2O_4$  :

15

C 62.49%, H 5.59%, N 9.72%

Found : C 62.86%, H 5.72%, N 9.72%

(3) Ethyl 2-hydroxy-5-methyl-3-(pyrrol-1-yl)benzoate  
mp : 67-68°C

20

IR (Nujol) : 1670, 1620, 1480  $cm^{-1}$

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.44 (3H, t, J=7.1Hz), 2.32 (3H, s), 4.43 (2H, q, J=7.1Hz), 6.3-6.4 (2H, m), 7.0-7.1 (2H, m), 7.29 (1H, s), 7.60 (1H, s), 11.20 (1H, s)

25

### Preparation 13

The following compounds were obtained according to a similar manner to that of Preparation 2.

30 (1) Ethyl 4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylate as an oil

IR (Neat) : 1725, 1605, 1595, 1555, 1495  $cm^{-1}$

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.32 (3H, t, J=7.1Hz), 1.57 (6H, s), 4.29 (2H, q, J=7.1Hz), 6.11 (1H, m), 6.28 (1H, t, J=3.3Hz), 7.12 (1H, t, J=7.9Hz), 7.43

35

(1H, dd, J=1.5, 7.8Hz), 7.49 (1H, m), 7.85 (1H, dd, J=1.5, 8.0Hz)

5 (2) Ethyl 8-methanesulfonyl-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylate as an oil  
NMR (DMSO-d<sub>6</sub>, δ) : 1.39 (3H, t, J=7Hz), 1.63 (6H, s), 3.34 (3H, s), 4.36 (2H, q, J=7Hz), 6.19 (1H, m), 6.29 (1H, m), 7.71 (1H, m), 7.96 (1H, d, J=2.2Hz), 8.38 (1H, d, J=2.2Hz)

10

(3) Ethyl 8-acetylamino-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylate  
mp : 139-140°C (from AcOEt-iPE)

15 IR (Nujol) : 3350, 1720, 1660, 1610, 1550 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ) : 1.32 (3H, t, J=7Hz), 1.56 (6H, s), 2.06 (3H, s), 4.29 (2H, q, J=7Hz), 6.11 (1H, m), 6.30 (1H, m), 7.25 (1H, m), 7.61 (1H, d, J=2.4Hz), 8.01 (1H, d, J=2.4Hz), 10.10 (1H, s)

20 (4) Ethyl 4,4-dimethyl-8-methyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylate as an oil

IR (Neat) : 1720, 1610, 1590, 1555, 1490 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 1.40 (3H, t, J=7.1Hz), 1.63 (6H, s), 2.36 (3H, s), 4.37 (2H, q, J=7.1Hz), 6.00 (1H, m), 6.30 (1H, m), 7.07 (1H, m), 7.27 (1H, s), 7.36 (1H, m)

25

#### Preparation 14

30 The following compounds were obtained according to a similar manner to that of Preparation 3.

(1) 4,4-Dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylic acid

35 mp : 162-167°C (ethyl acetate-hexane)  
IR (Nujol) : 2700-2100, 1700, 1675, 1605, 1590 cm<sup>-1</sup>

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.56 (6H, s), 6.10 (1H, m), 6.28 (1H, t, 3.0Hz), 7.09 (1H, t,  $J=7.9$ Hz), 7.43 (1H, dd,  $J=1.5$ , 7.8Hz), 7.48 (1H, m), 7.80 (1H, dd,  $J=1.5$ , 7.8Hz)

5

(2) 8-Methanesulfonyl-4,4-dimethyl-4H-pyrrolo[2,1-c]-[1,4]benzoxazine-6-carboxylic acid

mp : 197-198 (from AcOEt-iPE)

IR (Nujol) : 1720, 1600, 1565  $\text{cm}^{-1}$

10 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.62 (6H, s), 3.32 (3H, s), 6.18 (1H, m), 6.36 (1H, m), 7.69 (1H, m), 7.95 (1H, d,  $J=2.2$ Hz), 8.33 (1H, d,  $J=2.2$ Hz)

Elemental Analysis Calcd. for  $\text{C}_{15}\text{H}_{15}\text{NO}_5\text{S}$  :

C 56.06%, H 4.70%, N 4.35%

15 Found : C 55.53%, H 4.90%, N 4.21%

(3) 8-Acetylamino-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxylic acid

mp : 245°C (dec.) (from AcOEt-iPE)

20 IR (Nujol) : 3320, 1720, 1690, 1605, 1550  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.55 (6H, s), 2.05 (3H, s), 6.10 (1H, m), 6.30 (1H, m), 7.23 (1H, m), 7.61 (1H, d,  $J=2.4$ Hz), 7.97 (1H, d,  $J=2.4$ Hz), 10.05 (1H, s)

Elemental Analysis Calcd. for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4$  :

25 C 63.99%, H 5.37%, N 9.33%

Found : C 63.79%, H 5.44%, N 9.18%

(4) 8-Methyl-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxylic acid

30 mp : 158-161°C

IR (Nujol) : 2700-2100, 1685, 1615, 1490  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.54 (6H, s), 2.33 (3H, s), 6.08 (1H, m), 6.26 (1H, m), 7.27 (1H, m), 7.45 (1H, dd,  $J=1.5$ , 3.0Hz), 7.66 (1H, d,  $J=1.7$ Hz), 12.7 (1H, br s)

35

Example 1

A mixture of 8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c]-[1,4]benzoxazine-6-carboxylic acid (1.0 g) obtained in Preparation 3, 1,3-dicyclohexylcarbodiimide (743 mg),  
5 1-hydroxybenzotriazole hydrate (551 mg), and N,N-dimethylformamide (15 ml) was stirred at room temperature for 1 hour. To this mixture was added a solution of 1-azabicyclo[2,2,2]octyl-3-amine (0.50 g) in N,N-dimethylformamide (5 ml). After 10 minutes, the  
10 mixture was treated with triethylamine (0.50 ml) and then stirred at room temperature for 14 hours. The precipitate formed was filtered and the filtrate was evaporated in vacuo. The residue was diluted with water, made basic with 3N aqueous sodium hydroxide solution, and extracted  
15 three times with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. Column chromatography on silica gel (10% methanol-chloroform) of the residue gave an oil (1.18 g), which was treated with hydrogen  
20 chloride in ethanol and crystallized from methanol-ether to give N-(1-azabicyclo[2,2,2]oct-3-yl)-8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide hydrochloride (1.02 g).

mp : 157-165°C

25 IR (Nujol) : 3360, 2550, 1650, 1585, 1530, 1485 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.55 (3H, s), 1.60 (3H, s),

1.65-2.20 (5H, m), 3.00-3.80 (6H, m),

4.29 (1H, m), 6.15 (1H, m), 6.31 (1H, m),

7.32 (1H, d, J=2Hz), 7.60 (1H, m),

30 7.97 (1H, d, J=2Hz), 8.59 (1H, d, J=6Hz)

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

35

- (1) Endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxamide hydrochloride  
mp : 164-166°C (methanol-ether)  
5 IR (Nujol) : 3400, 2700, 2550, 1650, 1590, 1525, 1490 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ) : 1.60 (6H, s), 2.00-2.80 (8H, m),  
2.64 (3H, m), 3.80-4.00 (3H, m), 6.16 (1H, m),  
6.32 (1H, m), 7.33 (1H, d, J=2Hz), 7.60 (1H, m),  
10 7.98 (1H, d, J=2Hz), 8.34 (1H, d, J=4Hz)
- (2) 8-Chloro-4,4-dimethyl-N-[[4-(4-fluorobenzyl)-morpholin-2-yl]methyl]-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxamide hydrochloride  
15 mp : 216-222°C (methanol-ether)  
IR (Nujol) : 3350, 2400, 1660, 1590, 1530 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ) : 1.58 (3H, s), 1.61 (3H, s),  
2.80-3.80 (6H, m), 4.05 (3H, m),  
4.34 (2H, br s), 6.16 (1H, m), 6.31 (1H, m),  
20 7.29 (2H, t, J=9Hz), 7.49 (1H, d, J=2Hz),  
7.61 (1H, s), 7.71 (2H, t, J=9Hz),  
8.02 (1H, d, J=2Hz), 8.38 (1H, m),  
12.03 (1H, br s)
- (3) N-[2-(diethylamino)ethyl]-8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide hydrochloride  
25 mp : 203-205°C (ethanol-ether)  
IR (Nujol) : 3400, 2650, 1650, 1590, 1510, 1490 cm<sup>-1</sup>  
30 NMR (DMSO-d<sub>6</sub>, δ) : 1.25 (3H, t, J=7Hz), 1.63 (6H, s), 3.12-3.24 (6H, m), 3.69 (2H, q, J=6Hz),  
6.14 (1H, m), 6.31 (1H, t, J=3Hz),  
7.48 (1H, d, J=2Hz), 7.59 (1H, m),  
8.00 (1H, d, J=2Hz), 8.43 (1H, t, J=6Hz)

Example 3

Starting from 8-chloro-4H-pyrrolo[2,1-c][1,4]-benzoxazine-6-carboxylic acid obtained in Preparation 9, the following compounds were obtained according to a similar manner to that of Example 1.

(1) N-(1-azabicyclo[2,2,2]oct-3-yl)-8-chloro-4H-pyrrolo-[2,1-c][1,4]benzoxazine-6-carboxamide hydrochloride  
mp : >250°C (methanol-ether)

IR (Nujol) : 3300, 2470, 1660, 1640, 1595, 1550,  
1495 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.60-2.20 (5H, m),  
3.10-3.40 (5H, m), 3.63 (1H, t, J=10Hz),  
4.27 (1H, m), 5.29 (2H, s), 6.12 (1H, m),  
6.33 (1H, m), 7.30 (1H, d, J=2Hz), 7.62 (1H, m),  
7.97 (1H, d, J=2Hz), 8.70 (1H, d, J=6Hz),  
10.42 (1H, br s)

(2) Endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-8-chloro-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide hydrochloride

mp : 213-218°C (methanol-ether)

IR (Nujol) : 3400, 1660, 1650, 1585, 1530 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.00-2.80 (8H, m), 2.65 (3H, m),  
3.70-4.10 (3H, m), 5.31 (2H, s), 6.14 (1H, m),  
6.34 (1H, m), 7.33 (1H, d, J=2Hz), 7.63 (1H, m),  
7.99 (1H, d, J=2Hz), 8.49 (1H, d, J=5Hz), 10.62  
(1H, m)

Example 4

Starting from 1,8-dichloro-4,4-dimethyl-4H-pyrrolo-[2,1-c][1,4]benzoxazine-6-carboxylic acid obtained in Preparation 10, the following compound was obtained according to a similar manner to that of Example 1.

N-(1-azabicyclo[2,2,2]oct-3-yl)-1,8-dichloro-4,4-



dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide  
hydrochloride

mp : 232-237°C (ethanol-ether)

IR (Nujol) : 3250, 2550, 2450, 1645, 1590, 1540  $\text{cm}^{-1}$

5 NMR (DMSO- $d_6$ ) : 1.52 (3H, s), 1.57 (3H, s),  
1.65-2.20 (5H, m), 3.00-3.40 (5H, m), 3.63 (1H,  
br t, J=13Hz), 4.28 (1H, m), 6.24 (1H, d,  
J=4Hz), 6.42 (1H, d, J=4Hz), 7.44 (1H, d,  
J=2Hz), 8.17 (1H, d, J=2Hz), 8.64 (1H, d,  
10 J=6Hz), 10.47 (1H, s)

#### Example 5

A solution of 4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]-  
benzoxazine-6-carboxylic acid (0.50 g),  
15 1-hydroxybenzotriazole hydrate (314 mg), and  
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
hydrochloride (393 mg) in N,N-dimethylformamide (6 ml) was  
stirred at 0°C for 30 minutes. 1-Azabicyclo[2,2,2]octyl-  
3-amine dihydrochloride (450 mg) and a solution of  
20 N-methylmorpholine (600 mg) in N,N-dimethylformamide (2  
ml) were added and the mixture was stirred at 0°C for 2  
hours and then at room temperature for 14 hours. The  
reaction mixture was diluted with water, made basic with  
3N aqueous sodium hydroxide solution, and extracted three  
25 times with dichloromethane. The organic layer was washed  
with water and brine, dried over anhydrous sodium sulfate,  
and evaporated in vacuo. Column chromatography on silica  
gel (15% methanol-chloroform) of the residue gave an oil  
(0.72 g), which was treated with hydrogen chloride in  
30 dioxane and crystallized from methanol-ether to give  
N-(1-azabicyclo[2,2,2]oct-3-yl)-4,4-dimethyl-4H-pyrrolo-  
[2,1-c][1,4]benzoxazine-6-carboxamide hydrochloride (589  
mg).

mp : 235-238°C (methanol-ether)

35 IR (Nujol) : 3370, 1645, 1585, 1535  $\text{cm}^{-1}$

NMR (DMSO-d<sub>6</sub>, δ) : 1.56 (3H, s), 1.62 (3H, s),  
1.65-2.30 (5H, m), 3.00-3.40 (5H, m), 3.60 (1H,  
m), 4.32 (1H, m), 6.12 (1H, m), 6.29 (1H, t,  
J=3.2Hz), 7.13 (1H, t, J=7.9Hz), 7.36 (1H, dd,  
J=1.5, 7.8Hz), 7.51 (1H, m), 7.80 (1H, dd,  
J=1.5, 7.9Hz), 8.50 (1H, d, J=6.4Hz), 10.99 (1H,  
br s)

### Example 6

The following compounds were obtained according to a  
similar manner to that of Example 5.

(1) Endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-4,4-  
dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-  
carboxamide hydrochloride

mp : >250°C (methanol-ether)

IR (Nujol) : 3470, 1635, 1590, 1520 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.61 (6H, s), 2.00-2.80 (8H, m),  
2.65 (3H, m), 3.80-4.10 (3H, m), 6.14 (1H, m),  
6.30 (1H, t, J=3.3Hz), 7.13 (1H, t, J=7.9Hz),  
7.42 (1H, dd, J=1.6, 7.8Hz), 7.50 (1H, m), 7.79  
(1H, dd, J=1.5, 7.9Hz), 8.26 (1H, d, J=4.4Hz),  
10.70 (1H, br s)

(2) Endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-4,4-  
dimethyl-8-methyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-  
6-carboxamide hydrochloride

mp : 214-216°C (dec.) (methanol-ethyl acetate)

IR (Nujol) : 3450, 1630, 1590 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.60 (6H, s), 2.0-2.9 (11H, m),  
2.33 (3H, s), 3.6-4.0 (3H, m), 6.12 (1H, m),  
6.28 (1H, m), 7.26 (1H, d, J=1.5Hz), 7.49 (1H,  
dd, J=1.4, 2.9Hz), 7.66 (1H, d, J=1.8Hz), 8.25  
(1H, d, J=4.4Hz), 10.9 (1H, br s)

(3) N-(1-azabicyclo[2,2,2]oct-3-yl)-4,4-dimethyl-8-methyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide hydrochloride

mp : >250°C (methanol-ether)

5 IR (Nujol) : 3350, 1640, 1590 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.54 (3H, s), 1.60 (3H, s),  
1.6-2.3 (6H, m), 2.33 (3H, s), 3.0-3.4 (4H, m),  
3.5-3.6 (1H, m), 4.2-4.6 (1H, m), 6.11 (1H, dd,  
J=1.4, 3.4Hz), 6.27 (1H, m), 7.19 (1H, d,  
10 J=1.4Hz), 7.48 (1H, dd, J=1.4, 2.9Hz), 7.65 (1H,  
d, J=1.6Hz), 8.45 (1H, d, J=6.4Hz), 10.93 (1H,  
br s)

#### Example 7

15 A solution of 8-chloro-4,4-dimethyl-4H-pyrrolo-[2,1-c][1,4]benzoxazine-6-carboxylic acid (278 mg), diphenyl phosphoroazidate (275 mg), and triethylamine (101 mg) in toluene (5 ml) was heated at 80°C for 1.5 hours. After cooling, the reaction mixture was evaporated in  
20 vacuo and the residue was dissolved in N,N-dimethylformamide (3 ml). Endo-8-methyl-8-azabicyclo-[3,2,1]oct-3-ylamine (320 mg) and triethylamine (400 mg) were added to the solution. After stirring for 18 hours, the solution was diluted with 1N aqueous sodium hydroxide  
25 solution and extracted three times with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. Column chromatography on silica gel (20% methanol-chloroform) of the residue gave 1-(8-chloro-4,4-  
30 dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazinyl)-3-(endo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)urea (110 mg).

mp : 230-236°C

IR (Nujol) : 3250, 1640, 1610, 1545 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.61 (6H, s), 1.50-2.10 (8H, m),  
35 2.16 (3H, s), 3.01 (2H, br s), 3.74 (1H, m),

6.10 (1H, m), 6.25 (1H, t, J=3.2Hz), 7.00 (1H, d, J=5.7Hz), 7.35 (1H, d, J=2.4Hz), 7.50 (1H, m), 8.05 (1H, d, J=2.4Hz), 8.17 (1H, s)

5     Example 8

The following compound was obtained according to a similar manner to that of Example 7.

3-(1-Azabicyclo[2,2,2]oct-3-yl)-1-(8-chloro-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazinyl)urea as an oil  
10     IR (Film) : 3250, 1680, 1605, 1540 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ) : 1.62 (6H, s), 1.65-2.30 (5H, m),  
3.00-3.60 (5H, m), 3.92 (1H, m), 4.14 (1H, m),  
6.08 (1H, m), 6.25 (1H, t, J=3.2Hz), 7.38 (1H,  
15     m), 7.49 (1H, m), 8.01 (1H, m), 8.63 (1H, d, J=5.5Hz), 8.72 (1H, s)

Example 9

A mixture of 8-methanesulfonyl-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxylic acid (0.96 g),  
20     1,3-dicyclohexylcarbodiimide (0.62 g),  
1-hydroxybenzotriazole hydrate (0.46 g) in  
N,N-dimethylformamide (20 ml) was stirred at ambient  
temperature for one hour. To the resulting mixture was  
25     added a mixture of endo-8-methyl-8-azabicyclo[3.2.1]octyl-3-amine dihydrochloride (0.54 g), and triethylamine (0.91 g) in N,N-dimethylformamide (10 ml) and the reaction  
mixture was stirred at ambient temperature for 16 hours.  
The mixture was evaporated in vacuo and the residue was  
30     dissolved in a mixture of ethyl acetate and water. The  
separated organic layer was washed with brine and dried  
over magnesium sulfate, and evaporated in vacuo. The  
residue was subjected on column chromatography on alumina  
being eluted with a mixture of chloroform and methanol  
35     (99:1) and the fraction containing the desired product was

evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and diisopropyl ether to give endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-8-methanesulfonyl-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide (0.49 g).

mp : 173-174°C

IR (Nujol) : 3400, 1650, 1590, 1520  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.68 (6H, s), 1.74-2.17 (8H, m), 2.20 (3H, s), 3.04 (2H, m), 3.30 (3H, s), 4.01 (1H, m), 6.22 (1H, m), 6.37 (1H, m), 7.70 (1H, m), 7.99 (1H, d,  $J=2.2\text{Hz}$ ), 8.13 (1H, d,  $J=5.7\text{Hz}$ ), 8.30 (1H, d,  $J=2.2\text{Hz}$ )

Elemental Analysis Calcd. for  $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}\cdot\text{H}_2\text{O}$  :

C 59.85%, H 6.77%, N 9.10%

Found : C 59.84%, H 6.88%, N 9.06%

#### Example 10

The following compound was obtained according to a similar manner to that of Example 9.

Endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-8-acetylamino-4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-carboxamide

mp : 215-216°C (from AcOEt-iPE)

IR (Nujol) : 3400, 3260, 1685, 1640, 1600, 1560, 1510  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.65 (6H, s), 1.65-2.20 (8H, m), 2.06 (3H, s), 2.19 (3H, s), 3.05 (2H, br s), 4.05 (1H, m), 6.15 (1H, m), 6.32 (1H, m), 7.25 (1H, m), 7.73 (1H, d,  $J=2.5\text{Hz}$ ), 8.10 (1H, d,  $J=2.5\text{Hz}$ ), 8.15 (1H, d,  $J=6.2\text{Hz}$ ), 10.11 (1H, s)

Elemental Analysis Calcd. for  $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_3\cdot 1/5\text{H}_2\text{O}$  :

C 67.64%, H 7.19%, N 13.14%

Found : C 67.54%, H 7.39%, N 13.06%

Example 11

The following compound was obtained according to a similar manner to that of Example 1.

5           N-(1-azabicyclo[2,2,2]oct-3-yl)-8-methanesulfonyl-  
4,4-dimethyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-6-  
carboxamide hydrochloride

mp : >260°C (from methanol-ether)

IR (Nujol) : 3450, 3320, 2520, 1640, 1590, 1540 cm<sup>-1</sup>

10       NMR (DMSO-d<sub>6</sub>, δ) : 1.60 (3H, s), 1.64 (3H, s),  
1.65-2.25 (5H, m), 3.22 (3H, s), 3.08-3.70 (6H,  
m), 4.33 (1H, m), 6.19 (1H, m), 6.36 (1H, m),  
7.70 (1H, m), 7.79 (1H, d, J=2.1Hz), 8.29 (1H,  
d, J=2.1Hz), 8.71 (1H, d, J=6.4Hz)

15       Elemental Analysis Calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>SHCl·1/2H<sub>2</sub>O :

C 55.62%, H 6.15%, N 8.84%

Found : C 55.22%, H 6.48%, N 8.43%

20

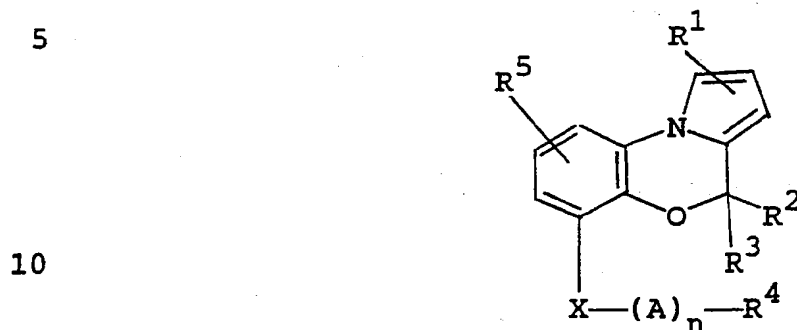
25

30

35

## C L A I M S

1. A compound of the formula :



wherein R<sup>1</sup> is hydrogen or halogen,

R<sup>2</sup> and R<sup>3</sup> are each hydrogen or lower alkyl,

R<sup>4</sup> is lower alkylamino;

azabicyclo(C<sub>5</sub>-C<sub>12</sub>)alkyl which may be substituted with lower alkyl; or

N-containing heterocyclic group which may be substituted with

ar(lower)alkyl optionally substituted with halogen,

R<sup>5</sup> is hydrogen, halogen, lower alkyl, acyl or acylamino,

X is  $\begin{array}{c} | \\ \text{CONH-} \end{array}$  or  $\begin{array}{c} | \\ \text{NHCONH-} \end{array}$ ,

A is lower alkylene and

n is an integer of 0 or 1,

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

R<sup>4</sup> is lower alkylamino;

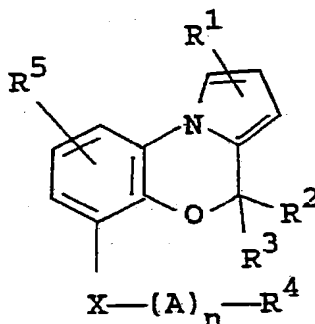
azabicyclo(C<sub>7</sub>-C<sub>10</sub>)alkyl which may substituted with lower alkyl; or

saturated 5- or 6-membered heteromonocyclic

group containing 1 or 2 nitrogen atom(s) and/or

1 or 2 oxygen atom(s) which may be substituted  
with benzyl optionally substituted with  
halogen, and  
5  $R^5$  is hydrogen, halogen, lower alkyl,  
lower alkanesulfonyl or lower alkanoylamino.

3. A compound of claim 2, wherein  
 $R^2$  and  $R^3$  are each lower alkyl and  
n is an integer of 0.
- 10 4. A compound of claim 3, wherein  
 $R^4$  is azabicyclo( $C_7-C_{10}$ )alkyl which may be  
substituted with lower alkyl.
- 15 5. A compound of claim 4, wherein  
 $R^1$  is hydrogen and  
 $R^5$  is halogen.
- 20 6. A compound of claim 5, wherein X is CONH-.
7. A process for preparing a compound of the formula :



wherein  $R^1$  is hydrogen or halogen,  
 $R^2$  and  $R^3$  are each hydrogen or lower alkyl,  
 $R^4$  is lower alkylamino;  
azabicyclo( $C_5-C_{12}$ )alkyl which may be  
35 substituted with lower alkyl; or



N-containing heterocyclic group

which may be substituted with

ar(lower)alkyl optionally substituted  
with halogen,

5  $R^5$  is hydrogen, halogen, lower alkyl, acyl or  
acylamino,

X is  $\begin{array}{c} | \\ \text{CONH-} \end{array}$  or  $\begin{array}{c} | \\ \text{NHCONH-} \end{array}$ ,

A is lower alkylene and

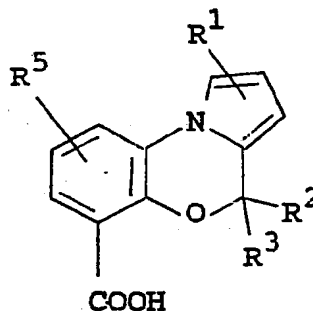
10 n is an integer of 0 or 1,

or its salt

which comprises

(1) reacting a compound of the formula :

15

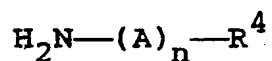


20

or its reactive derivative at the carboxy group

25

or its salt with a compound of the formula :

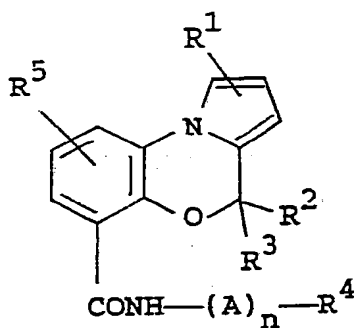


or its reactive derivative at the amino group

30

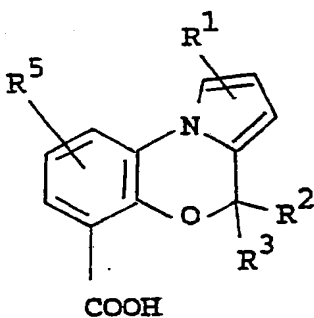
or its salt to give a compound of the formula :

35

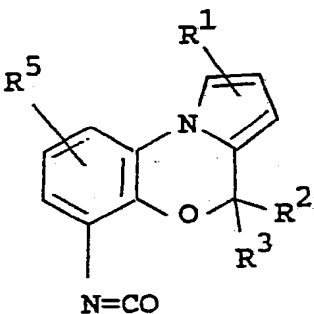


10 or its salt, in which  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , A and n are each as defined above, or

(2) subjecting a compound of the formula :

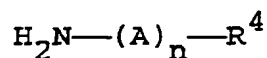


or its reactive derivative at the carboxy group  
or its salt to rearrangement reaction to give  
a compound of the formula :

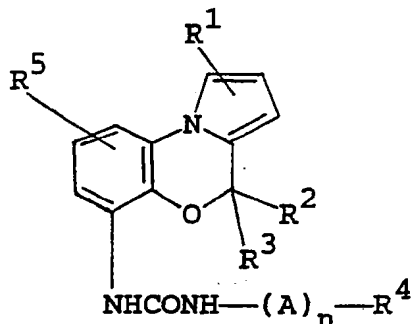


and then reacting a compound of the formula :

35

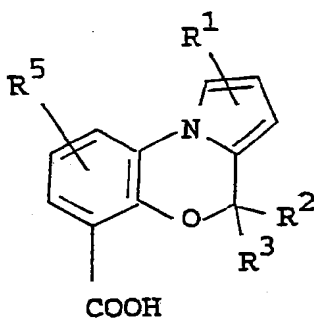


or its reactive derivative at the amino group  
or its salt to give a compound of the formula :



or its salt, in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , A and n are  
each as defined above.

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
9. A method for the treatment of gastrointestinal disorders which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.
10. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.
11. A compound of the formula :



wherein R<sup>1</sup> is hydrogen or halogen,  
R<sup>2</sup> and R<sup>3</sup> are each hydrogen or lower alkyl, and  
R<sup>5</sup> is hydrogen, halogen, lower alkyl, acyl or  
acylamino,  
and pharmaceutically acceptable salt thereof.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 92/01220

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D498/04; C07D453/02; C07D451/02; A61K31/535 /(C07D498/04, 265:00, 209:00)		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP,A,0 313 393 (YOSHITOMI) 26 April 1989 *Page1,11-12,18-20*	1-10
A	EP,A,0 419 397 (A/S FERROSAN) 27 March 1991 *Complete specification*	1-10
A	EP,A,0 407 137 (YOSHITOMI) 9 January 1991 *Complete specification*	1-10
A	US,A,4 035 495 (IVO JIRKOVSKY) 12 July 1977 cited in the application *Complete specification*	1-11
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search 21 DECEMBER 1992		Date of Mailing of this International Search Report 21.01.93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer LUYTEN H.W.

Form PCT/ISA/210 (second sheet) (January 1985)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 92/01220

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 9 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

JP 9201220  
SA 64795

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 21/12/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0313393	26-04-89	JP-A- 1207290	21-08-89
		CA-A- 1304082	23-06-92
		US-A- 4892872	09-01-90
		JP-A- 2028182	30-01-90
EP-A-0419397	27-03-91	AU-A- 6341490	08-04-91
		CA-A- 2066696	09-03-91
		WO-A- 9103475	21-03-91
		EP-A- 0491770	01-07-92
EP-A-0407137	09-01-91	CA-A- 2020315	04-01-91
		JP-A- 3279372	10-12-91
US-A-4035495	12-07-77	None	

EPO FORM P047

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82